Abstract

Background
In addition to scalability, human embryonic stem cells (hESCs) have the unique advantage of allowing their directed differentiation toward lineage-specific cells.

Objectives
This study tested the feasibility of leveraging the properties of hESCs to generate clinical-grade cardiovascular progenitor cells and assessed their safety in patients with severe ischemic left ventricular dysfunction.

Methods
Six patients (median age 66.5 years [interquartile range (IQR): 60.5 to 74.7 years]; median left ventricular ejection fraction 26% [IQR: 22% to 32%]) received a median dose of 8.2
million (IQR: 5 to 10 million) hESC-derived cardiovascular progenitors embedded in a fibrin patch that was epicardially delivered during a coronary artery bypass procedure. The primary endpoint was safety at 1 year and focused on: 1) cardiac or off-target tumor, assessed by imaging (computed tomography and fluorine-18 fluorodeoxyglucose positron emission tomography scans); 2) arrhythmias, detected by serial interrogations of the cardioverter-defibrillators implanted in all patients; and 3) alloimmunization, assessed by the presence of donor-specific antibodies. Patients were followed up for a median of 18 months.

Results

The protocol generated a highly purified (median 97.5% [IQR: 95.5% to 98.7%]) population of cardiovascular progenitors. One patient died early post-operatively from treatment-unrelated comorbidities. All others had uneventful recoveries. No tumor was detected during follow-up, and none of the patients presented with arrhythmias. Three patients developed clinically silent alloimmunization. All patients were symptomatically improved with an increased systolic motion of the cell-treated segments. One patient died of heart failure after 22 months.

Conclusions

This trial demonstrates the technical feasibility of producing clinical-grade hESC-derived cardiovascular progenitors and supports their short- and medium-term safety, thereby setting the grounds for adequately powered efficacy studies. (Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure [ESCORT]; NCT02057900)

Central Illustration
Key Words
cardiovascular progenitor cells; embryonic stem cells; heart failure; tissue engineering

Abbreviations and Acronyms
CT, computed tomography; DSA, donor-specific antibody; EF, ejection fraction; ESC, embryonic stem cell; hESC, human embryonic stem cell; HLA, human leukocyte antigen; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; PET, positron emission tomography; SSEA-1, stage-specific embryonic antigen-1
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